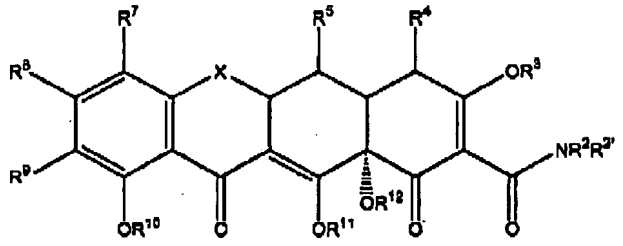
U.S.S.N.: 10/692563 Examiner: Sabiha Naim Qazi
Attorney Docket No.: PAZ-114CP2 Group Art Unit: 1616

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of the claims and listing of the claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{3}, R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, or a prodrug moiety, ~~or linked to R^{9} to form a ring~~;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{7} is aryl~~a malaria interacting moiety~~;

R^{9} is hydrogen;

R^{8} is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof, such that malaria is treated or prevented in said subject.

2. **(Cancelled)**

3. **(Previously Presented)** The method of claim 1, wherein R^2, $R^{2'}$, R^3, R^8, R^{10}, R^{11}, and R^{12} are hydrogen; R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are alkyl, and X is $CR^6R^{6'}$.

4. **(Previously Presented)** The method of claim 3, wherein R^5, R^6, and $R^{6'}$ are each hydrogen.

5. **(Previously Presented)** The method of claim 3, wherein R^5 is hydroxy or a prodrug moiety, R^6 is methyl and $R^{6'}$ is hydrogen.

6.-28. **(Cancelled)**

29. **(Currently Amended)** The method of claim ~~1~~28, wherein R^7~~said aryl group~~ is substituted or unsubstituted phenyl.

30. **(Currently Amended)** The method of claim 29, wherein R^7 ~~said phenyl group~~ is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkyl, alkenyl, alkynyl, or aryl.

31. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with ~~said alkoxy group~~ is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with ~~said alkyl group is~~ substituted or substituted methyl, ethyl, propyl, butyl or pentyl.

33. **(Currently Amended)** The method of claim 32, wherein said substituted or substituted methyl, ethyl, propyl, butyl or pentyl ~~alkyl group~~ is substituted with an amino, carbocyclic or heterocyclic group.

34. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with ~~said acyl group is~~ acetyl.

35. **(Currently Amended)** The method of claim 28, wherein R^7 ~~said aryl group~~ is substituted or unsubstituted heteroaryl.

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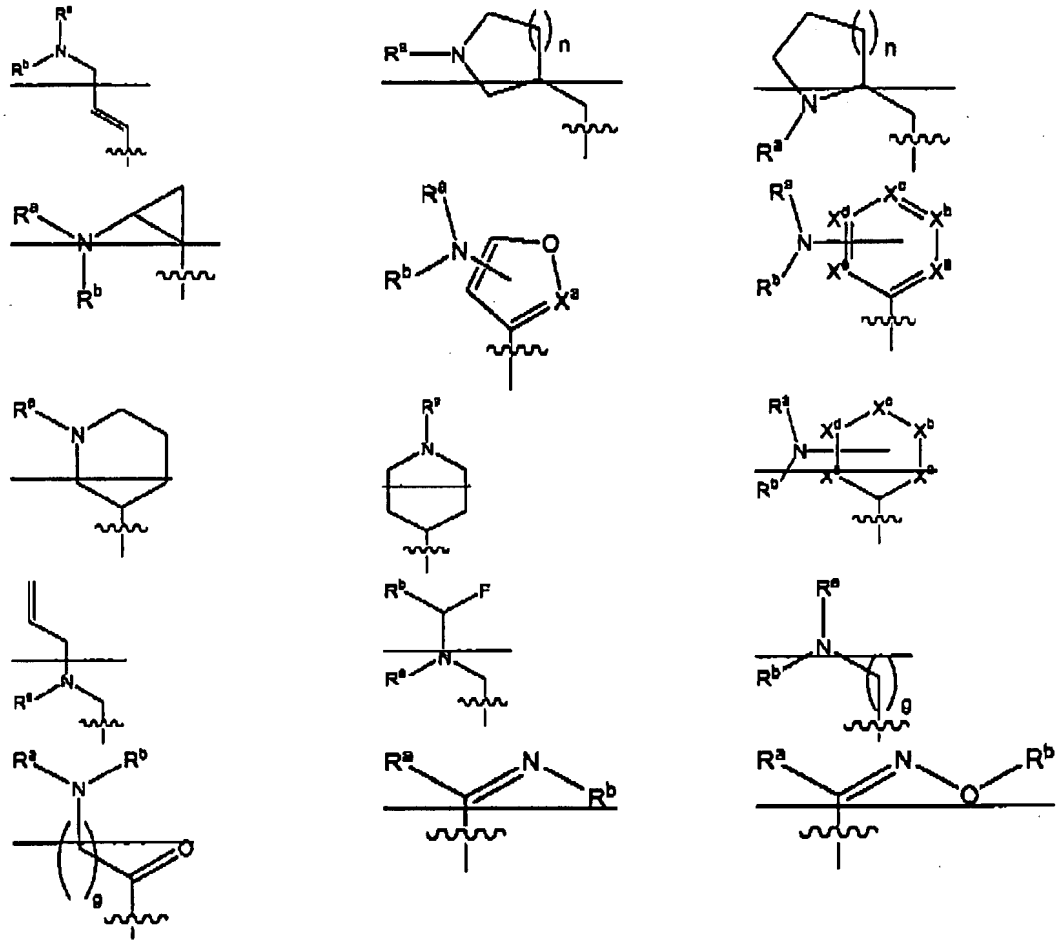
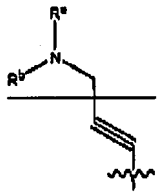
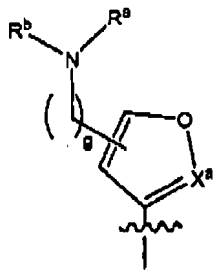
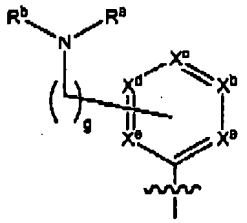
36. **(Currently Amended)** The method of claim 35, wherein ~~said heteroaryl~~R^7 is thienyl, imidazolyl, pyrolyl, pyridinyl, furanyl, pyrimidinyl, or benzofuranyl.

Claims 37-41 **(Canceled).**

42. **(Currently Amended)** The method of claim 1, wherein R^7 ~~said malaria interacting moiety~~ comprises an ionizable nitrogen atom.

43. **(Currently Amended)** The method of claim 26, wherein said malaria interacting moiety is selected from the group consisting of:



wherein:

R^a and R^b are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

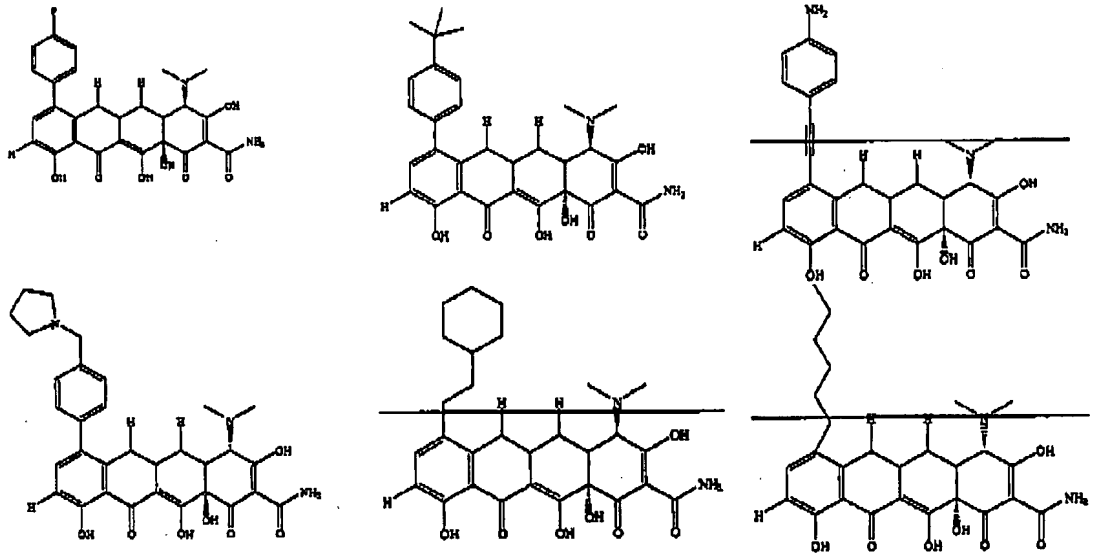
g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

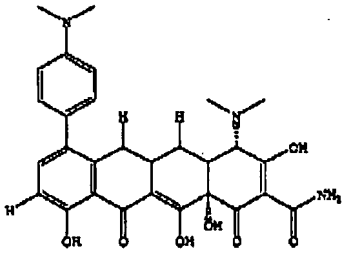
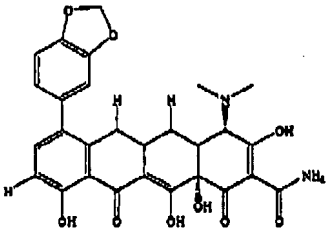
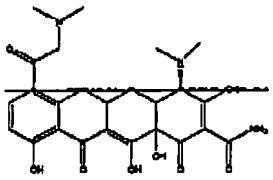
n is 0, 1, 2, or 3; and

X^a, X^b, X^c, X^d, and X^e are each independently optionally substituted carbon, oxygen, nitrogen, or sulfur.

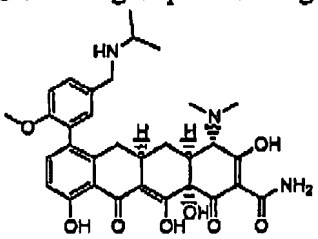
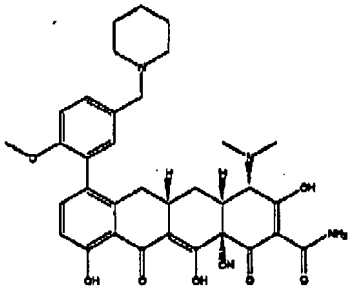
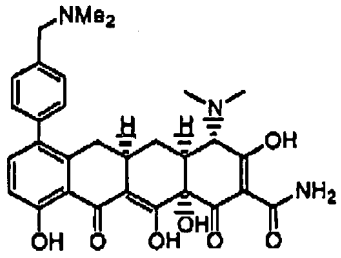
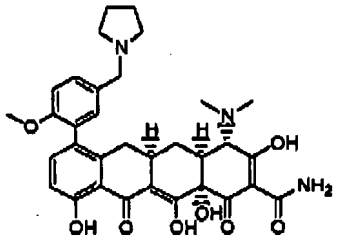
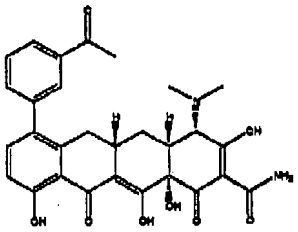
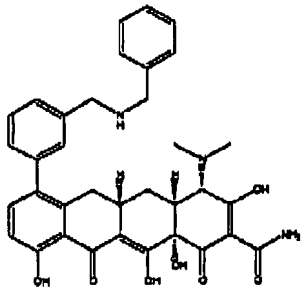
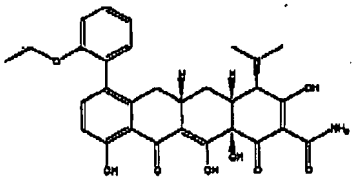
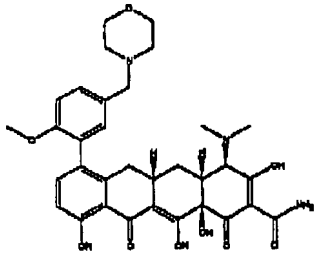
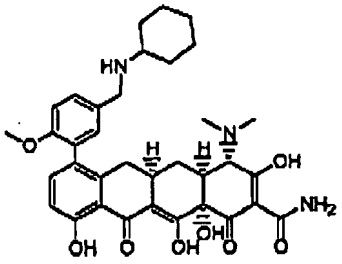
Claims 44-47 **(Cancelled)**.

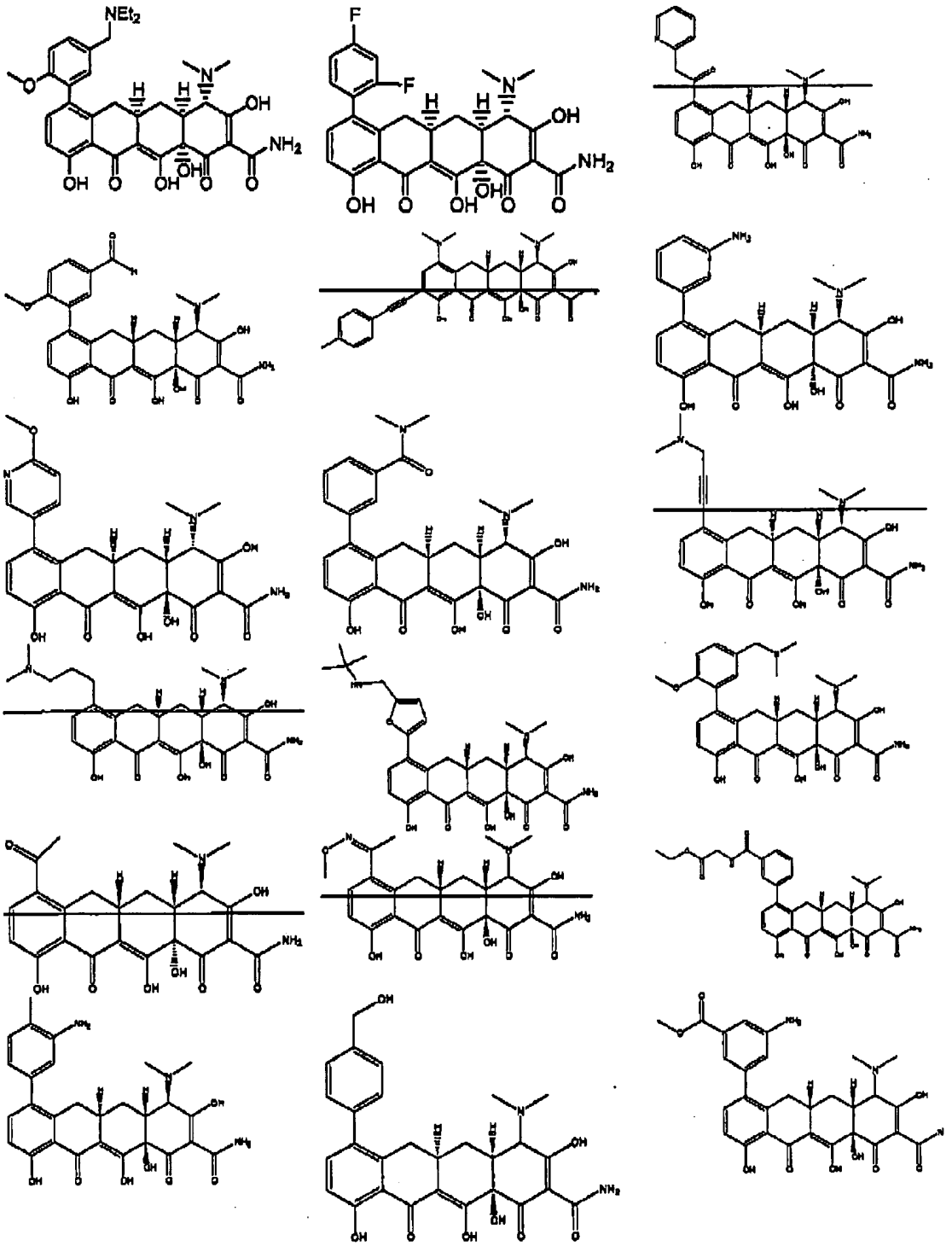
48. **(Currently Amended)** The method of claim 1, wherein said compound is selected from the group consisting of:

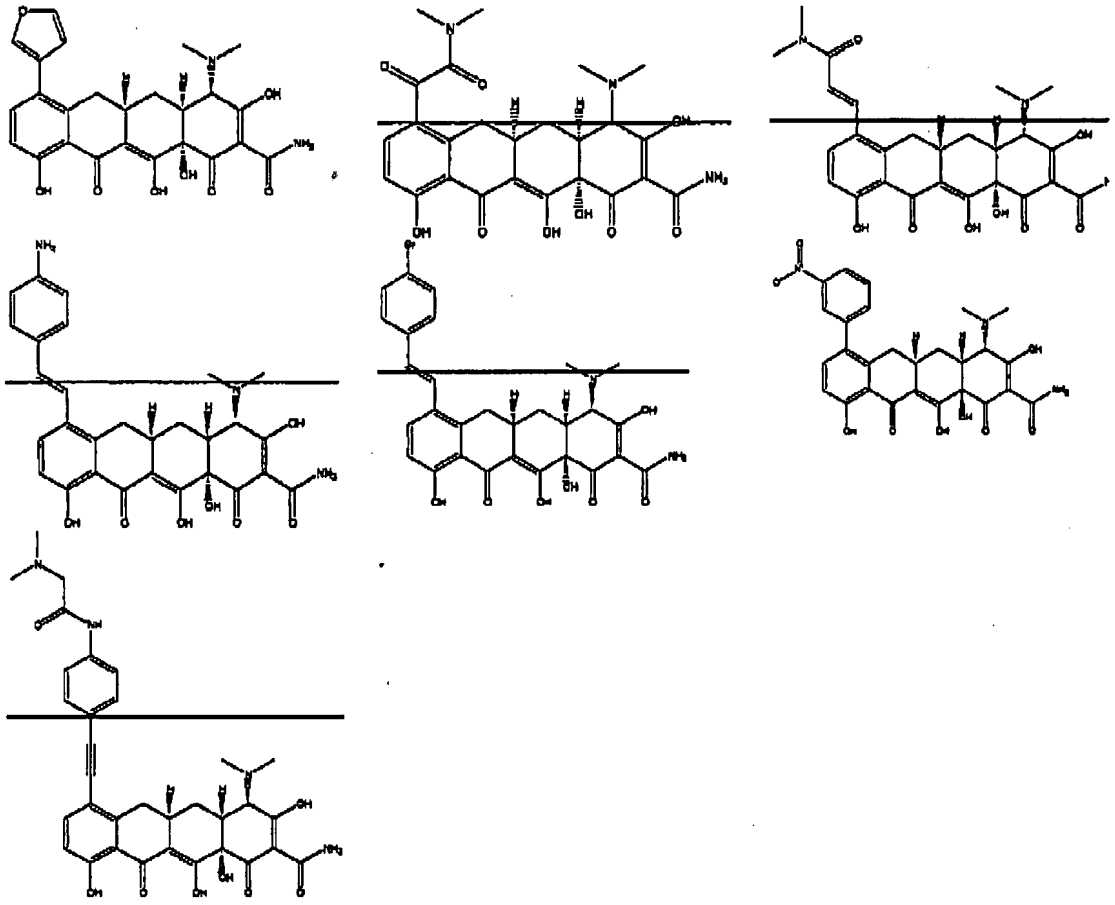


49. **(Currently Amended)** The method of claim 1, wherein said compound is selected from the group consisting of:





50. **(Currently Amended)** The method of claim ~~2~~ 1, wherein said compound is a compound shown in Table 1 or Table 2.

51. **(Original)** The method of claim 1, wherein said subject is a human.

52. **(Original)** The method of claim 1, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.

53. **(Original)** The method of claim 52, wherein said anti-microbial gram positive activity is greater than about 0.05 μg/ml.

54. **(Original)** The method of claim 53, wherein said anti-microbial gram positive activity is greater than about 5 μg/ml.

55. **(Original)** The method of claim 1, wherein said substituted tetracycline compound in non-antibacterial.

56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 μg/ml or greater.

57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

60. **(Original)** The method of claim 59, wherein said substituted tetracycline compound has an MIC or 5 nM or less.

61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.

62. **(Original)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, proguanil, and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.

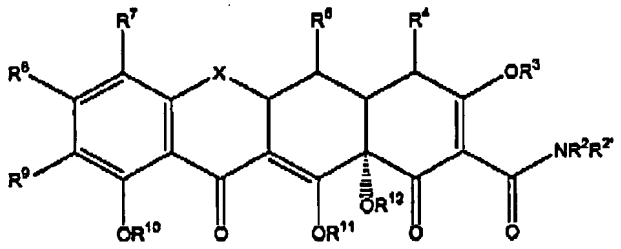
63. **(Original)** The method of claim 1, further comprising administering a supplementary compound.

64. **(Original)** The method of claim 63, wherein said supplementary compound treats a symptom selected from the group consisting of: headache, malaise, anemia, splenomegaly, and fever.

65. **(Original)** The method of claim 64, wherein said supplementary compound is an anti-malarial compound.

66. **(Original)** The method of claim 65, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^2, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^3, R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, or a prodrug moiety~~, or linked to R^9 to form a ring~~;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

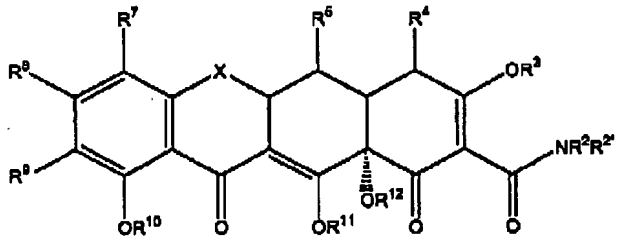
R^7 is aryla ~~malaria interacting moiety~~;

R^9 is hydrogen;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

68. **(Original)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^6$;

R^2, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^3, R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, or a prodrug moiety~~, or linked to R^9 to form a ring~~;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

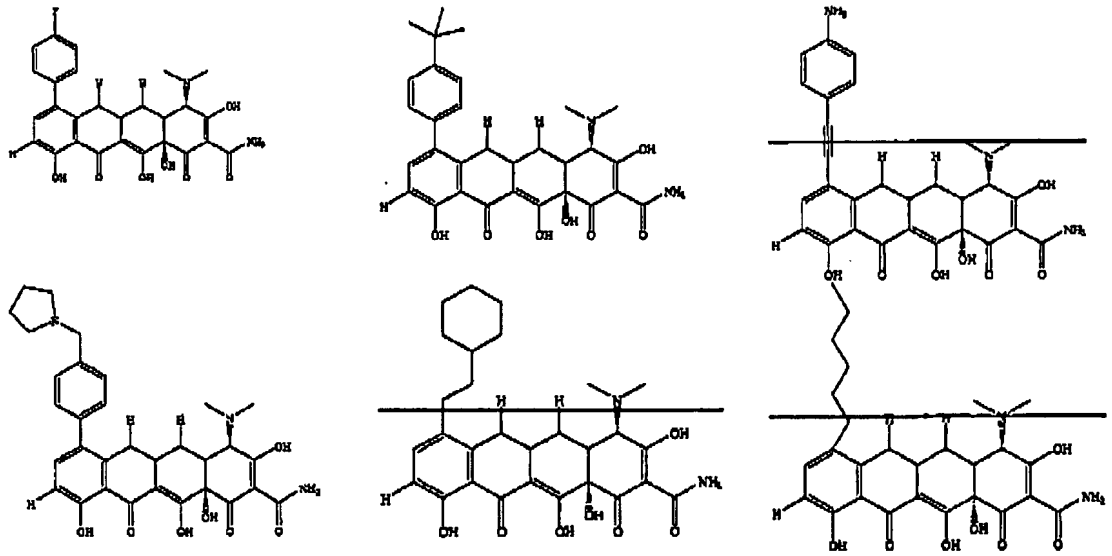
R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is aryl~~a malaria interacting moiety~~;

R^9 is hydrogen;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

70. **(Currently Amended)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:



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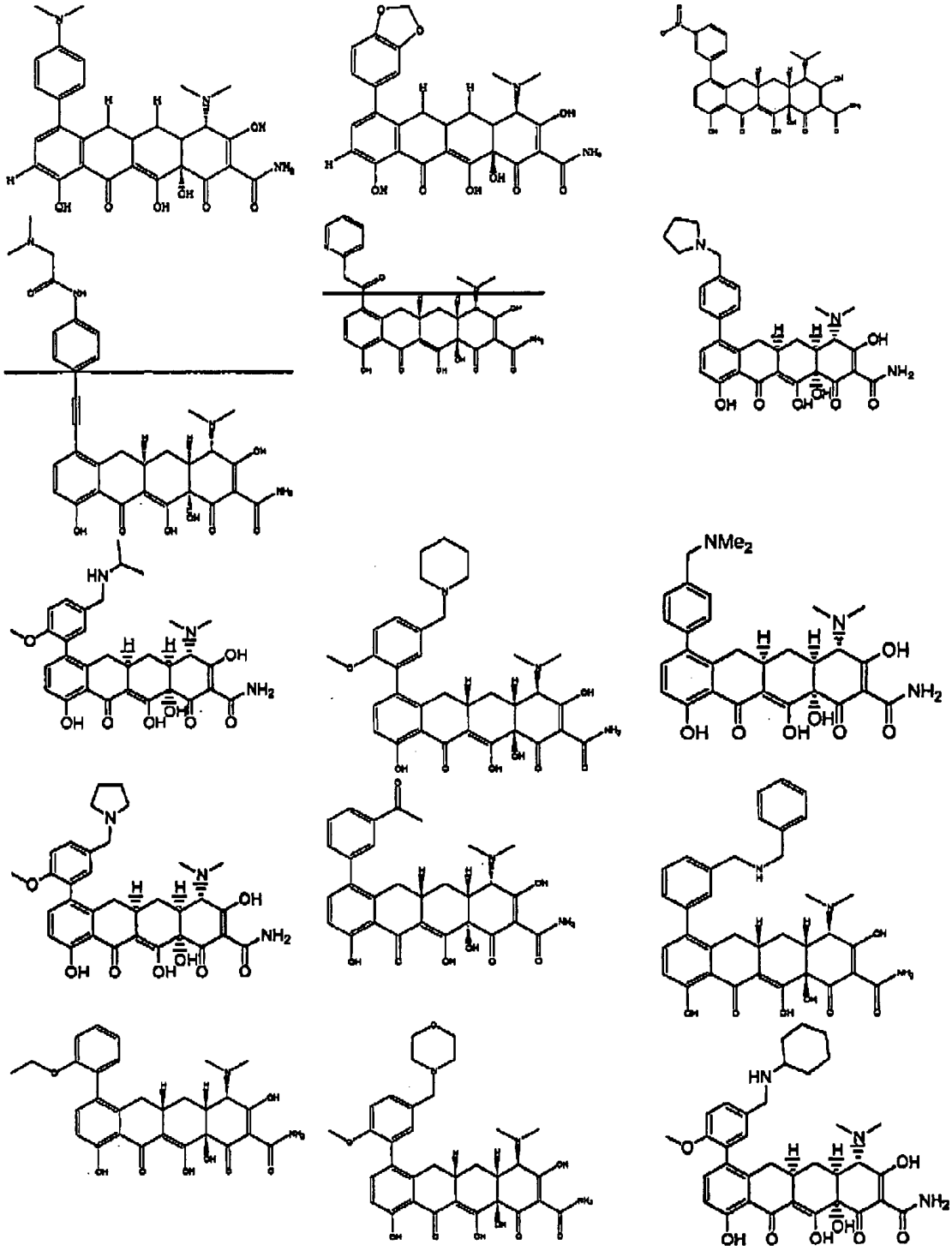
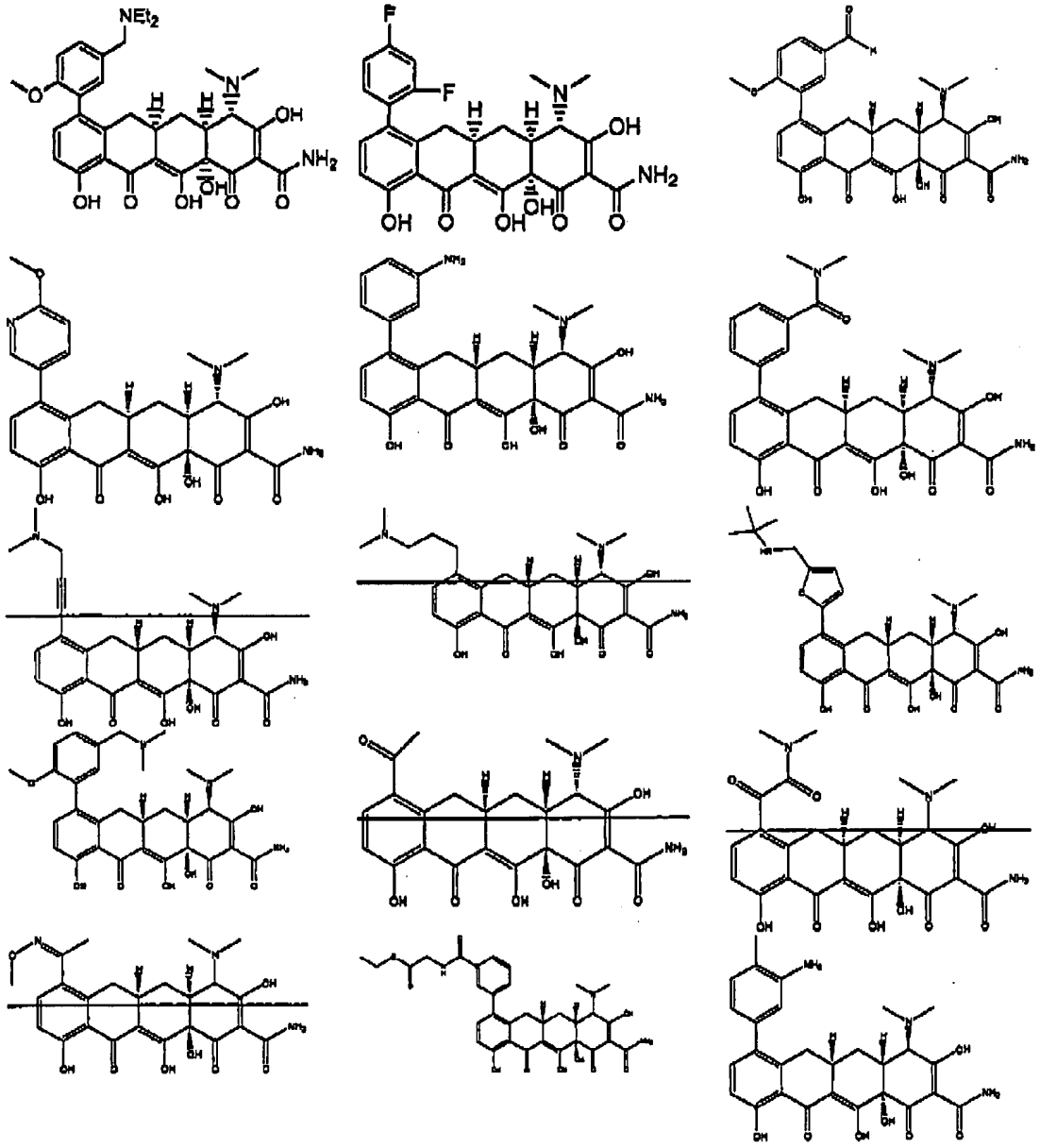
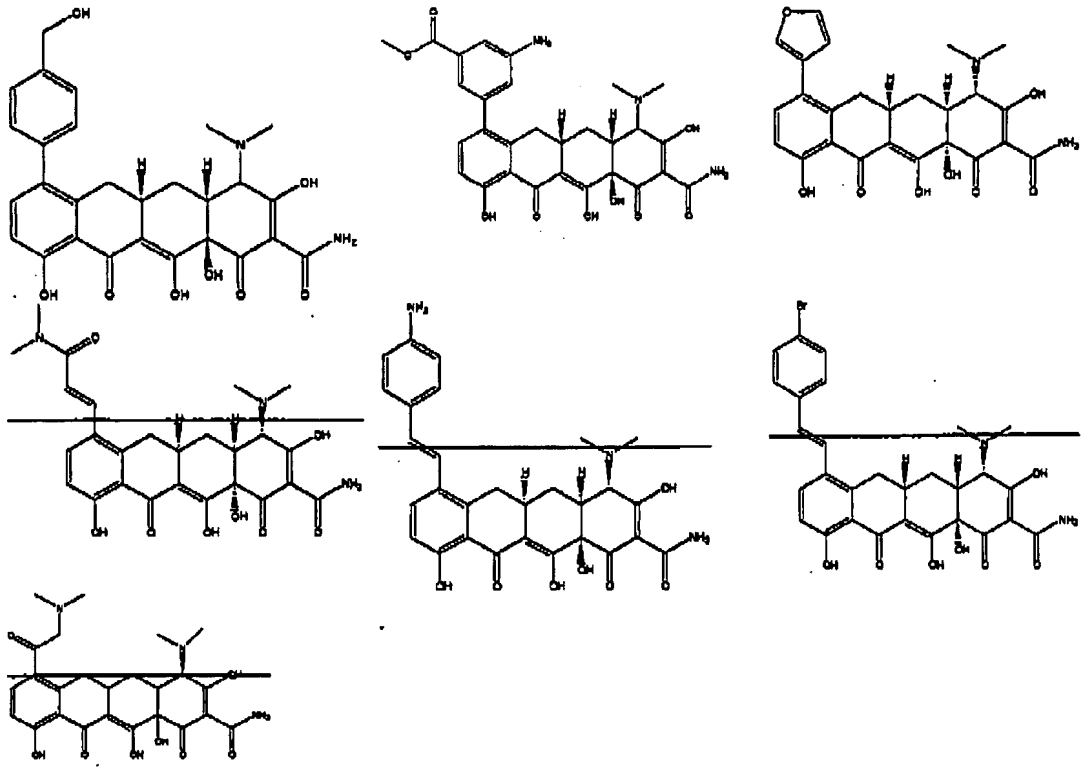






71. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.

72. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is non-antibacterial.

73. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound is has anti-microbial gram positive activity.

74. **(Original)** The method of claim 73, wherein said anti-microbial gram positive activity is greater than about 0.05 μg/ml.

75. **(Original)** The method of claim 74, wherein said anti-microbial gram positive activity is greater than about 5 μg/ml.

76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25 μg/ml or greater.

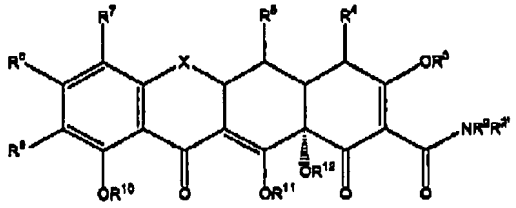
77. **(Original)** The method of claim 67 or 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Original)** The method of claim 79, wherein said substituted tetracycline compound has an MIC or 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{3}, R^{11} and R^{12} are each hydrogen, or a pro-drug moiety;

R^{10} is hydrogen, or a prodrug moiety~~, or linked to R^{9} to form a ring~~;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

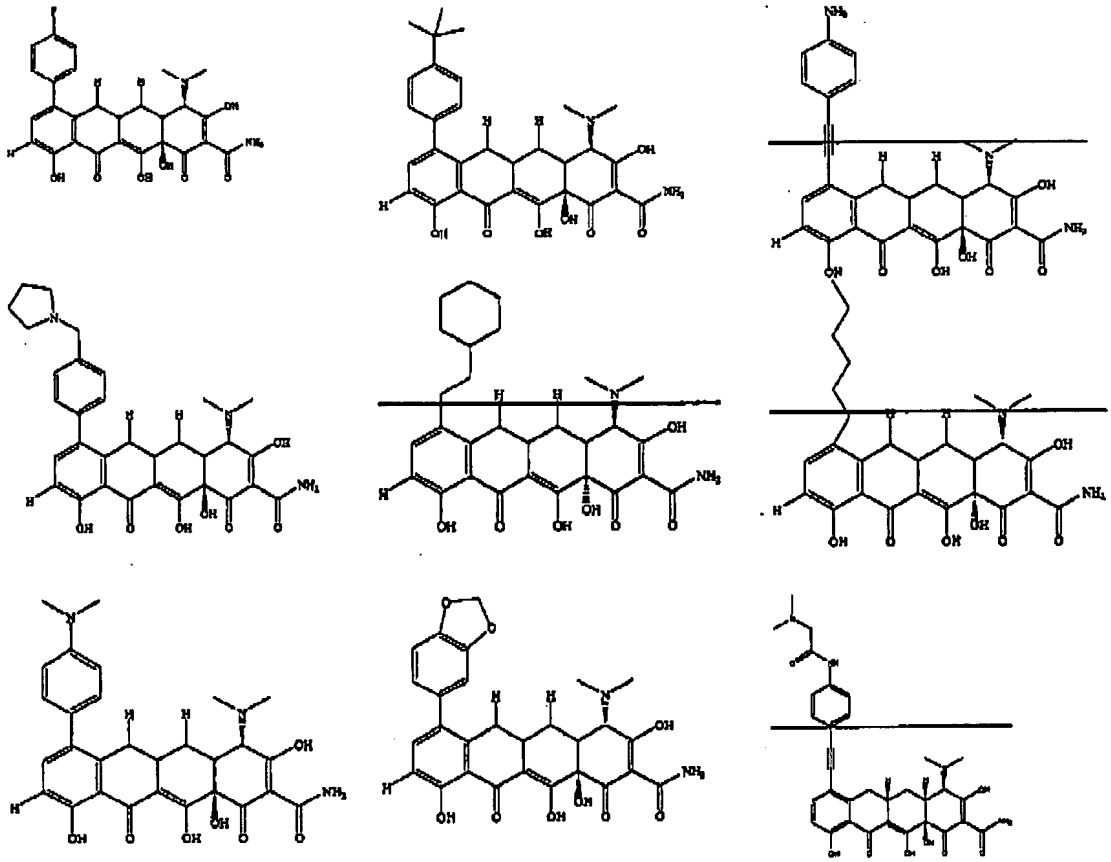
R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is aryl~~a malaria interacting moiety~~;

R^9 is hydrogen;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and pharmaceutically acceptable salts thereof.

82. **(Currently Amended)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is selected from the group consisting of:



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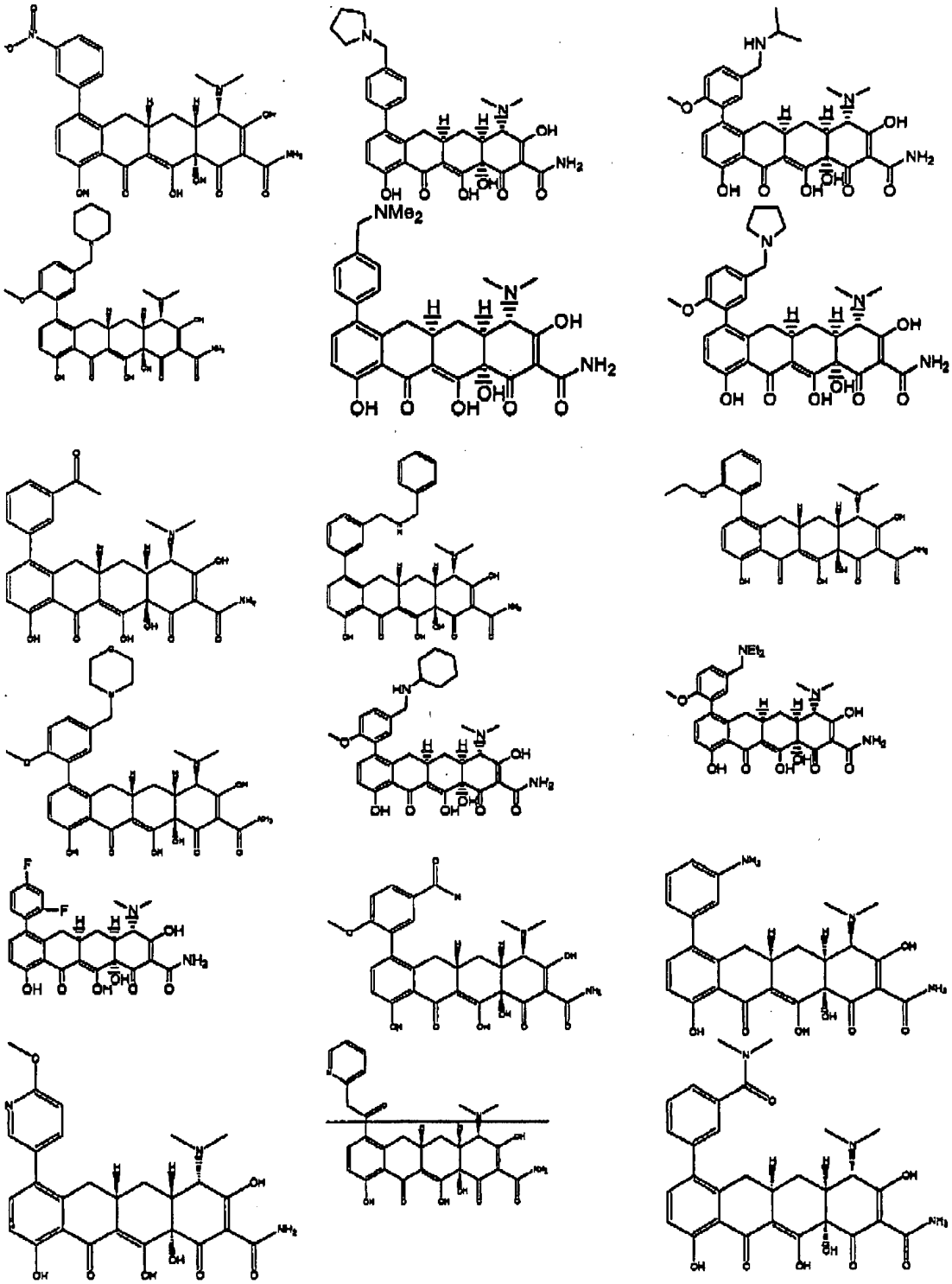

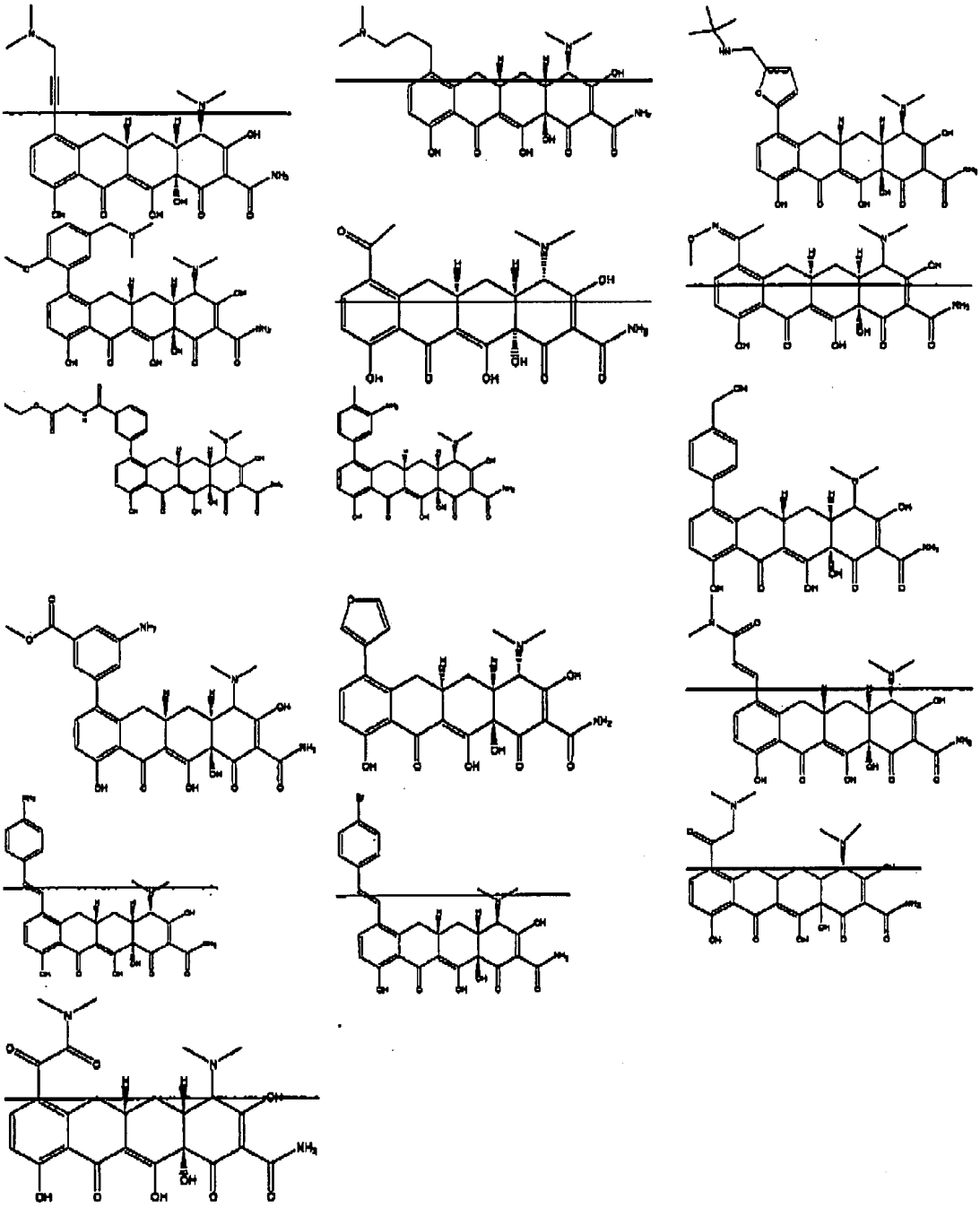

83. **(Original)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is a compound shown in Table 1 or Table 2.

84. **(Original)** The pharmaceutical composition of claim 81, further comprising a secondary agent.

85. **(Original)** The pharmaceutical composition of claim 84, wherein the secondary agent is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. **(Cancelled)**

87. **(Previously Presented)** The method of claim 1, wherein the substituted tetracycline compound is